REMARKS

Applicants respectfully request reconsideration. Claims-1, 4, 5, 8-14, 20-33 and 35 were previously pending in this application. By this amendment, Applicants are canceling claim 4 without prejudice or disclaimer. Claims 1 and 5 have been amended. As a result, claims 1, 5, 8-14, 20-33 and 35 are pending for examination with claim 1 being an independent claim. Claim 1 was amended to add the limitation of the elected claims that the non-nucleic acid adjuvant is an immune stimulating adjuvant. As a result, claim 4 is canceled herewith. Claim 1 was also amended to specifically exclude one of the members of the group of immune stimulating adjuvants, saponins, which was originally in the markush group of claim 5. Claim 1 was also amended to add the limitations found in original claims 15 and 16 now withdrawn. No new matter has been added.

Information Disclosure Statement

The Examiner has reminded the Applicants that under 37 C.F.R. § 1.98(b) an information disclosure statement (i.e. PTO-1449) is required for the application to be considered. This form was included with the information disclosure statement filed 09 February, 2004 (a copy of the return receipt postcard is attached as Exhibit 2). A copy of the original PTO-1449 is resubmitted herewith as Exhibit 3. It is respectfully requested that the examiner consider the information therein.

Rejections under 35 U.S.C. §112

Claims 1, 4, 5, 8-14, 20-33 and 35 stand rejected. Claim 4 has been canceled and the rejection no longer applies. Therefore, Claims 1, 5, 8-14, 20-33 and 35 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner states that "the disclosure fails to provide adequate guidance pertaining to those immune stimulating adjuvants...that can reasonably be expected to produce a synergistic immune response when combined with another adjuvant." We respectfully disagree.

Applicants have provided guidance in the specification for the use of immune stimulating adjuvants. Immune stimulating adjuvants are described in detail on page 6 lines 2-4, and further on page 19 lines 12-22. Immune stimulating adjuvants are defined as "an adjuvant that causes

activation of a cell of the immune system" and several representative examples are listed. Example 2 in the specification (page 53, line 30 – page 54 line 1) illustrates the synergistic effect of treatment with CpG-ODN and MPL, an immune-stimulating adjuvant. The corresponding data is shown in Figure 7.

In addition, Applicants have submitted a declaration of Dr. Heather Davis wherein Dr. Davis provides data demonstrating, as thoroughly described in the patent application, that the use of other immune stimulating adjuvants in combination with CpG-ODN results in a synergistic activation of the immune system. Specifically, the data show that the combination of various immune-stimulating adjuvants with CpG oligonucleotides, when used in mice, produces a significant shift from IgG1 toward IgG2a production, indicating a Th1 response.

These data demonstrate synergy between CpG-ODN and immune stimulating adjuvants, as thoroughly described in the patent application, and consisted with the data presented in Example 2 of the specification. The data represented in Exhibit 1 demonstrate that CpG oligonucleotides administered in combination with an immune-stimulating adjuvant produce an elevated immune response when compared to immunization with either CpG-ODN or immune-stimulating adjuvant alone. The data demonstrate an increase in overall IgG titer, an increase in the titer of IgG2a isotype, an increase in IgA production, and in most cases an increase in the ratio of IgG2a isotype to IgG1 isotype.

The results represented in Exhibit 1 were consistent in mice immunized with either HBsAg or Tetanus toxoid (TT), and a variety of immune-stimulating adjuvants. Immune stimulating adjuvants tested include Montanide ISA 720 (Seppic Inc.), Freund's incomplete adjuvant (FIA), cholera toxin (CT), E. coli heat-labile toxin (LT), cholera toxin subunit B (CTB), the B subunit of Escherichia coli heat labile enterotoxin (LTB), and various detoxified LT (LTK63, LTE112K, LTS61F, LTR192G, or LTA69G), and MF-59. Representative CpG-ODN included CpG-ODN 1826 (SEQ ID NO:86), CpG-ODN 7909 (SEQ ID NO:77), and CpG-ODN 1982, a non-CpG control of sequence 5' TCCAGGACTTCTCTCAGGTT 3'.

The examiner has indicated that the disclosure fails to provide adequate guidance regarding the "structural requirements of any given ISS-ODN." Initially Applicants wish to point out that in the office action of June 30, 2004, the Examiner refers to the CpG oligonucleotides as "ISS-ODN" (see page 3, paragraph two and page 4, line 1). Applicants would like to respectfully remind the Examiner that the invention specifies CpG

oligonucleotides, rather than ISS-ODN. It is Applicant's understanding that other investigators use the term ISS in a manner which is not always consistent with the use of CpG oligonucleotides by Applicants and as defined in the above-identified patent application.

Applicants have amended the claims to add the limitations that the CpG oligonucleotide have a prescribed length limitation (8-100 nucleotides) and a phosphate backbone modification. Such limitations were originally found in now withdrawn claims 15 and 16. It is unclear to Applicants why such dependent claims are withdrawn. The limitations found in these claims serve to provide more structural detail regarding the class of oligonucleotides useful according to the invention. It is respectfully requested that the amendment to the claims be entered.

The claimed CpG oligonucleotides all have the common structural property that they include an unmethylated CpG dinucleotide. This class of oligonucleotides is known and has been described extensively in patents and patent applications. It is the unmethylated CpG dinucleotide that confers the immune stimulating properties on the oligonucleotide. The context in which the CpG is found within the oligonucleotide (i.e. the identity of the surrounding nucleotides) has effects on the specific immune parameters that are induced or suppressed. Such effects render certain CpG oligonucleotides better at contributing to the production of an antigen specific immune responses than others. Although some CpG oligonucleotides are better than others, it is Applicants understanding that even the "poor" CpG oligonucleotides would still produce an antigen specific immune response under appropriate conditions such as dosage and formulation, particularly if they have a phosphorothioate modified backbone. Preferred oligonucleotides, phosphate backbone modifications, dosages and formulations are all appropriately described in the specification. Thus, the structural requirements are adequately described.

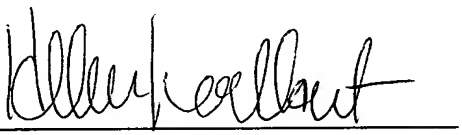
It is believed that this amendment is sufficient to overcome the rejection. Accordingly, withdrawal of the rejection of claims 1, 5, 8-14, 20-33 and 35 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number listed below.

Applicant hereby requests a One-Month Extension of Time to respond to the notice. A check for $110.00 is enclosed to cover the extension of time. Please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Heather L. Davis et al., Applicant(s)

By: 

Helen Lockhart, Ph.D.
Reg. No. 39,248
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone: (617) 646-8000

Docket No. C1039.70058US00
Date: October 25, 2004
x10/24/04

EXHIBIT 2

Serial No 10/023,909 File No C1039.70058US00 By: HCL

Title: USE OF NUCLEIC ACIDS CONTAINING UNMETHYLATED ...

Application of DAVIS ET AL WGS Date: NDD

The U.S. PTO Mail Room acknowledges receipt of the following on the date stamped hereon:

[ ] Mailing by Express Mail (37 CFR 1.10)
Express Mail Label No. _____
[ ] Patent Application
[ ] Non-provisional [ ] Provisional
Incl. _____ pages, (pgs) Specification,
(pgs) Abstract, (pgs) Claims (- claims)
[ ] Design Patent Application
[ ] Declaration(s)_____
[ ] Drawings _____ Sheet(s) (FIGS._____
[ ] Formal [ ] Informal
[ ] Utility Patent Application Transmittal
[ ] Fee calculation sheet (x2)
[ ] CPA Transmittal
[ ] Verified Statement claiming small entity status
[ ] Request for Approval and Entry of Formal Drawings

[ ] Provisional Application Cover Sheet
[ ] Multiple Dependent Claim Fee Sheet
[X] Inf. Discl. Statement, PTO Form 1449
[X] References Cited
[ ] Priority Document(s) #_____
[ ] Copy of Notice to File Missing Parts
[ ] Amendment/Response
[ ] Petition for Ext. of Time (x2)
[ ] Issue Fee Transmittal
[ ] Assignment and Coversheet
[ ] Notice of Appeal
[ ] Brief (x3)
[ ] Check for $_____ Check #____
[X] Transmittal Letter (x2)
[ ] Cert. of Mailing under 37 CFR 1.8(a)

[ ] Other 2 BOXES OF REFERENCES

DATE MAILED FEBRUARY 6, 2004

EXHIBIT 3

FORM PTO-1449/A and B (Modified)	APPLICATION NO.: 10/033,909	ATTY. DOCKET NO.: C1039.70058US00
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: 12/18/2001	CONFIRMATION NO.: 8458
	APPLICANT: Heather L. Davis et al.	
Sheet 1 of 3	GROUP ART UNIT: 1648	EXAMINER: Jeffrey S. Parkin

U.S. PATENT DOCUMENTS

Examiner's Initials	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or of issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
	A1	6,194,388	B1	Krieg et al.	02-27-2001
	A2	6,207,646	B1	Krieg et al.	03-27-2001
	A3	6,214,806	B1	Krieg et al.	04-10-2001
	A4	6,218,371	B1	Krieg et al.	04-17-2001
	A5	6,225,292	B1	Raz et al.	05-01-2001
	A6	6,239,116	B1	Krieg et al.	05-29-2001
	A7	6,339,068		Krieg et al.	01/15/2002
	A8	6,406,705	B1	Davis et al.	06-18-2002
	A9	6,429,199	B1	Krieg et al.	08-06-2002
	A10	6,498,148	B1	Raz	12/24/2002
	A11	6,514,948	B1	Raz, et atl	02/04/2003
	A12	6,534,062	B2	Krieg, et al.	03/18/2003
	A13	6,552,006	B2	Raz et al.	04/22/2003
	A14	6,562,798	B1	Schwartz	05/13/2003
	A15	6,589,940	B1	Raz et al.	07/08/2003
	A16	6,610,661	B1	Carson et al.	08/26/2003
	A17	6,653,292	B1	Krieg et al.	11/25/2003
	A18	US 2001/0046967		Van Nest	11/29/2001
	A19	US 2002/0028784		Van Nest	03/11/2002
	A20	US 2002/0042387		Raz et al.	04/11/2002
	A21	US 2002/0055477	A1	Nest et al	05/09/2002
	A22	US 2002/0086839		Raz et al.	07/04/2002
	A23	US 2002/0098199	A1	Van Nest et al.	07/25/2002
	A24	US 2002/0107212	A1	Van Nest et al.	08/08/2002
	A25	US 2002/0142978	A1	Raz et al.	10/03/2002
	A26	US 2002/0156033	A1	Bratzler et al.	10/24/2002
	A27	US 2003/0022852		Van Nest et al.	1/30/2003
	A28	US 2003/0049266	A1	Fearon et al.	03/13/2003
	A29	US 2003/0050263	A1	Krieg et al.	03/13/2003
	A30	US 2003/0059773		Van Nest et al.	01/30/2003
	A31	US 2003/0064064		Dina	04/03/2003
	A32	US 2003/0078223	A1	Raz et al.	04/24/2003
	A33	US 2003/0092663	A1	Raz	05/15/2003
	A34	US 2003/0109469	A1	Carson et al	06/12/2003
	A35	US 2003/0119773	A1	Raz et al.	06/26/2003
	A36	US 2003/0125284		Raz et al.	07/03/2003

FORM PTO-1449/A and B (Modified)	APPLICATION NO.: 10/023,909	ATTY. DOCKET NO.: C1039.70058US00
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: 12/18/2001	CONFIRMATION NO.: 8458
	APPLICANT: Heather L. Davis et al.	
Sheet 2 of 3	GROUP ART UNIT: 1648	EXAMINER: Jeffrey S. Parkin

U.S. PATENT DOCUMENTS

Examiner's Initials	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or of issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
	A37	US 2003/0129251	A1	Van Nest et al.	07/10/2003
	A38	US 2003/0130217		Raz et al.	07/10/2003
	A39	US 2003/0133988	A1	Fearon et al.	07/17/2003
	A40	US 2003/0143213	A1	Raz et al.	07/37/2003
	A41	US 2003/0147870	A1	Raz et al.	08/07/2003
	A42	US 2003/0175731	A1	Fearon et al.	09/18/2003
	A43	US 2003/0176373		Raz et al.	09/18/2003
	A44	US 2003/0186921	A1	Carson et al.	10/02/2003
	A45	US 2003/0199466	A1	Fearon et al.	10/23/2003
	A46	US 2003/0203891		Goebel et al.	10/30/2003
	A47	US 2003/0212028	A1	Raz et al.	11/13/2003
	A48	US 2003/0216340	A1	Van Nest et al.	11/20/2003
	A49	US 2003/0232780		Carson et al.	12/18/2003
	A50	US 2004/0006034		Raz et al.	01/08/2004
	A51	US 2004/0009942		Van Nest et al.	01/15/2004

FOREIGN PATENT DOCUMENTS

Examiner's Initials	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document (not necessary)	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			
	B1	WO	99/11275	A2	Regents of the University of CA	03/11/1999	
	B2	WO	99/62923	A2	Dynavax Tech. Corp	12/09/1999	
	B3	WO	00/20039	A1	Regents of the University of CA	04/13/2000	
	B4	WO	00/62787	A1	Regents of the University of CA	10/26/2000	
	B5	WO	98/55609	A1	Regents of the University of CA	10/12/1998	
	B6	WO	00/21556	A1	Dynavax Tech. Corp	04/20/2000	
	B7	WO	01/02007	A1	Regents of the University of CA	01/11/2001	
	B8	WO	01/12223	A2	Dynavax Tech. Corp	02/01/2001	
	B9	WO	01/55341	A2	Regents of the University of CA	08/02/2001	
	B10	WO	01/68077	A2	Dynavax Tech. Corp	09/20/2001	
	B11	WO	01/68078	A2	Dynavax Tech. Corp	09/20/2001	
	B12	WO	01/68103	A2	Dynavax Tech. Corp	09/20/2001	
	B13	WO	01/68116	A2	Dynavax Tech. Corp	09/20/2001	
	B14	WO	01/68117	A2	Dynavax Tech. Corp	09/20/2001	

FORM PTO-1449/A and B (Modified)	APPLICATION NO.: 10/023,909	ATTY. DOCKET NO.: C1039.70058US00
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: 12/18/2001	CONFIRMATION NO.: 8458
	APPLICANT: Heather L. Davis et al.	
Sheet 3 of 3	GROUP ART UNIT: 1648	EXAMINER: Jeffrey S. Parkin

OTHER ART — NON PATENT LITERATURE DOCUMENTS

Examiner's Initials	Cite No	Include name of the author (in CAPITAL LETTERS) title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, relevant page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)	
	C1	Elkins, K. L., Rhinehart-Jones, T. R., et al., "Bacterial DNA containing CpG motifs stimulates lymphocyte-dependent protection of mice against lethal infection with intracellular bacteria." *J Immunol* 162:2291-2298, 1999.		
	C2	Freidag, B. L et al., "CpG oligodeoxynucleotides and interleukin-12 improve the efficacy of Mycobacterium bovis BCG vaccination in mice challenged with M. tuberculosis.: *Infect Immun* 68:2948-2953, 2000.		
	C3	Hayashi, T.et al., "Enhancement of innate immunity against Mycobacterium avium infection by immunostimulatory DNA is mediated by indoleamine 2,3-dioxygenase." *Infect Immun* 69:6156-6164, 2001.		
	C4	Juffermans, N. P. et al., "CpG oligodeoxynucleotides enhance host defense during murine tuberculosis." *Infect Immun* 70:147-152, 2002.		
	C5	Klinman, D. M. et al., "Repeated administration of synthetic oligodeoxynucleotides expressing CpG motifs provides long-term protection against bacterial infection. *Infect Immun* 67:5658-5663, 1999"		
	C6	Klinman, D. M., et al. Activation of the innate immune system by CpG oligodeoxynucleotides: immunoprotective activity and safety. *Springer Semin Immunopathol* 22:173-183, 2000		
	C7	Krieg, A. M., et al., "CpG motifs in bacterial DNA and their immune effect." *Annu Rev Immunol* 20:709-760, 2002.		
	C8	Lipford, G. B. et al. "Immunostimulatory DNA: sequence-dependent production of potentially harmful or useful cytokines." *Eur J Immunol* 27:3420-3426, 1997.		
	C9	Sedegah, M.et al. "Interleukin 12 induction of interferon g-dependent protection against malaria." *Proc Natl Acad Sci U S A* 91:10700-10702, 1994.		
	C10	Sethi, S. et al. "Postexposure prophylaxis against prion disease with a stimulator of innate immunity." *Lancet* 360:229-230, 2002.		
	C11	Stacey, K. J et al. "Immunostimulatory DNA as an adjuvant in vaccination against Leishmania major." *Infect Immun* 67:3719-3726, 1999		
	C12	Walker, P. S. et al. "Immunostimulatory oligodeoxynucleotides promote protective immunity and provide systemic therapy for leishmaniasis via IL-12- and IFN-g-dependent mechanisms." *Proc Natl Acad Sci U S A* 96:6970-6975, 1999.		
	C13	Zimmermann, S. et al., "CpG oligodeoxynucleotides trigger protective and curative Th1 responses in lethal murine leishmaniasis." *J Immunol* 160:3627-3630, 1998.		

EXAMINER	DATE CONSIDERED

#EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[NOTE - Must provide a copy of any patent, publication, other information listed, even if it was previously submitted to, or cited by, the U.S. Patent Office in an earlier application, unless the earlier application is identified by the IDS and is relied upon for an earlier filing date under 35 U.S.C. §120, and the copy was provided in the earlier application.]